Australian Government
Department of Health
Therapeutic Goods Administration

Biovigilance responsibilities of sponsors of biologicals

Australian requirements and recommendations

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TGA Health Safety Regulation

Contents

Summary

All sponsors of products regulated as biologicals under the biologicals framework are required to:

- Report serious threats to public health and serious and near serious adverse events related to the biological within the regulatory timeframes (see Reporting requirements)
- retain records pertaining to the reporting requirements and safety of the biological (see Record-keeping requirements)
- ensure that any request from the TGA for the provision of additional information related to the biological is answered fully and within the specified timeframe

In order to achieve this, sponsors should have a robust biovigilance system in place.

Reporting requirements for biological adverse events: a summary

Adverse event	Method of reporting	Reporting timeframe*
Serious threat to public health *An event or occurrence that represents a serious threat to public health*	In writing to: si.coordinator@health.gov.au	≤ 48 hours
Serious adverse event *An event or occurrence **that led** to the death, or serious deterioration in the state of health of a patient, a user of the biological or another person*	A number of forms and methods are available: electronic structured data preferred	≤ 10 calendar days
Near serious adverse event *An event or occurrence that, if it occurred again, **might lead** to the death, or serious deterioration in the state of health, of a patient, a user of the biological or another person*	A number of forms and methods are available: electronic structured data preferred	≤ 30 calendar days
Recalls, quality defects and contaminated or counterfeit biologicals	Human blood & tissues recall report form or email: recalls@health.gov.au	with the least possible delay

*Timeframes are in relation to when the sponsor becomes aware that there is an issue for which there is a reasonable possibility of causal relationship.

Introduction

This guidance is for all sponsors of products regulated as biologicals and does not apply to sponsors of biological medicines or other therapeutic goods that are not regulated as biologicals. It outlines the mandatory reporting and record-keeping requirements and offers recommendations on biovigilance best practice.

In this guidance, we use 'must' or 'required' to describe something you are **legally obliged** to do. We use 'should' to **recommend** an action that will assist you to meet your legal requirements. We refer to the TGA as 'we' or 'us', and to sponsors as 'you'.

Biovigilance

Biovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other problem related to biologicals. Biovigilance for biologicals is analogous to pharmacovigilance for medicines and devices vigilance for medical devices. Biovigilance is part of Australia's therapeutic product vigilance system.

Role of the TGA

We have established vigilance systems for collecting and evaluating information relevant to the benefit-risk balance of all therapeutic goods, including biologicals. We continually monitor the safety profile of therapeutic goods available in Australia and take appropriate action where necessary.

Identifying adverse events and serious threats to public health

An adverse event is any undesirable medical event that occurs during or after the administration or use of a biological. It is a harmful and unintended response and can be any unfavourable and unintended symptom, sign (for example, an abnormal laboratory finding), disease or injury that occurs related to the use of a biological.

For biovigilance, the TGA uses the term ***adverse event*** to mean an undesirable medical event for which there is at least a reasonable possibility of a causal relationship between the use of the biological and the event. Such adverse events are considered to be related events and are reportable in accordance with the timeframes and guidance in this document.

Adverse events may be associated with the biological itself or any aspect of the biological, such as the:

- solutions
- excipients
- other substances or materials
- packaging
- delivery systems

There are three types of adverse events:

1. serious adverse events
2. near serious adverse events
3. non-serious adverse events

Assessing relatedness or causality of an adverse event

The potential for adverse events related to a biological depends on several factors including the:

- origin of the biological (autologous or allogeneic)
- ability of cells constituting a biological to proliferate or differentiate
- ability of the biological to initiate an immune response
- life span of the biological in vivo
- site and mode of administration
- type and level of cell manipulation during production
- storage time and conditions
- out-of-specification findings identified during in-process testing of the biological

These factors should be taken into consideration when assessing causality.

All spontaneous reports of biologicals adverse events notified to you by health professionals, patients or consumers are considered to be related adverse events as they convey the suspicions of the person reporting the information (the 'primary source') that there is a causal relationship.

A **spontaneous** report is an unsolicited communication by a health professional or consumer to a sponsor, manufacturer, regulatory authority or other organisation (e.g. WHO) that describes one or more suspected adverse events in a patient who was given a biological.

For a report to be spontaneous, it should not be derived from a study or any organised data collection system where adverse event reporting is actively sought (solicited).

Stimulated reports are considered to be spontaneous. Stimulated reporting can occur as a result of:

- notification by a 'Dear Health Professional' letter
- publication in the press or on social media
- questioning of health professionals by company representatives
- communication from patient organisations to their members
- class action lawsuits.

Spontaneous reports are reportable in accordance with the guidance in this document, **unless**:

- the reporter specifically states that they believe the events to be unrelated or that a causal relationship can be excluded

AND

- you agree with this assessment

If you disagree with the primary source about the reasonable possibility of a causal relationship, then both opinions should be recorded in the adverse event report given to the TGA. You should include the criteria on which the assessment was made.

For non-spontaneous (or solicited) reports, for example those from post-ARTG inclusion studies and other post-marketing initiatives (depending on method of data collection), all events judged by the reporting health professional, the investigator, or you as having at least a possible causal relationship with the biological should be considered related adverse events and reported. Non-spontaneous reports of adverse events do not need to be reported if they are not suspected to be causally related to the biological.

There are different methods for determining causality, for example the *World Health Organisation Uppsala Monitoring Centre (WHO–UMC) system for standardised case causality assessment*.

Serious adverse events

The term ***serious adverse event*** for a biological relates to *'an event or occurrence that led to a death or serious deterioration in the state of health of a patient, a user of the biological or another person'*.

A serious adverse event for a biological is an adverse event for which one or more of the following is true:

- results in death
- is life-threatening
- requires inpatient hospitalisation
- prolongs existing hospitalisation
- results in persistent or significant disability or incapacity, including permanent impairment of a body function or permanent damage to a body structure
- necessitates medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure
- is a congenital anomaly or birth defect
- is a medically important event:
  - Events that make one of the outcomes above more likely, or that require intervention to prevent one of these outcomes
  - For example, events that require intensive treatment in an emergency department or at home but do not result in hospitalisation, such as allergic bronchospasm, a blood disorder or convulsions

Such events occurring in Australia must be reported to the TGA within ten days of the sponsor becoming aware of them (*Therapeutic Goods Regulations 1990*, Regulation 16AB(b)).

Near serious adverse events

The term ***near serious adverse event*** for a biological relates to '*an event or occurrence that, if it occurred again, might lead to the death, or serious deterioration in the state of health, of a patient, a user of the biological or another person*'.

A near serious adverse event for a biological is an adverse event which, **if it occurs again**, might result in one or more of the above outcomes for a serious adverse event. Timely intervention by a health practitioner may have prevented such an outcome from occurring. This category also includes the situation where testing or examination of the biological, or information supplied with the biological or scientific literature has indicated some factor that could lead to one or more of the above outcomes.

Such events occurring in Australia must be reported to the TGA within thirty days of the sponsor becoming aware of them (*Therapeutic Goods Regulations 1990*, Regulation 16AB(c)).

Non-serious adverse events

All adverse events that do not meet the definition of serious or near serious adverse events are considered to be non-serious adverse events (see Reporting non-serious adverse events).

Serious threat to public health

A ***serious threat to public health*** in relation to a biological is considered to exist when any new safety issue is identified which may change the benefit-risk assessment of the product and require action to eliminate or reduce the risk. The term '*public health'* in serious threat to public health does not signify the risk to the population (such as a communicable disease), but rather it refers to the risk of adverse events in future individual recipients of biologicals from the same donor.

Safety issues which may change the benefit-risk assessment of a biological include:

- a report of an unexpected or previously unknown serious or near serious adverse event
- a change in the nature, severity or frequency of expected (known) adverse events
- the identification of previously unknown risk factors
- the transmission of an infectious agent, including reactivation of any viral vector
- a signal of a possible teratogenic effect
  - A signal indicating a possible teratogenic effect may come from a cluster of cases of similar abnormal outcomes in clinical situations or from nonclinical data
- a signal of possible tumorigenicity
- unexpected lack of efficacy
- issues related to the raw materials used in the biological
- issues related to the delivery system used for the biological
- issues due to misinformation in the product documentation
- issues related to use outside the approved indication or intended use

A serious threat to public health must be reported to the TGA within 48 hours of the sponsor becoming aware of them (*Therapeutic Goods Regulations 1990*, Regulation 16AB(a)).

Analysis to identify serious threats to public health

We expect you to use your clinical and scientific judgement for discerning which products available in Australia and worldwide are likely to provide relevant safety information for your biological and in determining whether a safety issue is a serious threat to public health. It is anticipated that this may be more difficult for biologicals than for medicines or medical devices.

You may identify serious threats to public health related to a biological as a result of your ongoing review and analysis of all information pertinent to the benefit-risk assessment of the product, for example, from:

- signal detection activities
- review and analysis of adverse event reports
  - including adverse events which have occurred in a country other than Australia
- reports about unexpected lack of efficacy
- studies that impact on the evidence for efficacy

- major safety findings from newly completed
  - nonclinical studies
  - post-ARTG inclusion studies
  - clinical trials
- other post-market activities
- the scientific or medical literature
- action taken by an overseas regulatory agency, such as:
  - withdrawal or suspension of the availability of the product
  - addition of a contraindication, warning or precaution statement to the product documentation or label
  - modification of an existing contraindication, warning or precaution for safety reasons
  - modification or removal of an indication or intended use for safety reasons

Your reporting requirements

What you must report

You must report:

- serious threats to public health
- serious and near-serious adverse events in Australia, regardless of whether
  - they are expected or unexpected
  - you disagree with the reporter's assessment of a possible causal association
  - the biological was used in accordance with the approved indications or intended use (that is, report in overdose, off-label use, misuse, administration error or occupational exposure)
  - another person has reported the serious or near serious adverse event; in this case you should inform us that it is likely to be a duplicate of a previously submitted report, and provide us with as many details as possible to aid in identifying the duplicate, including the TGA reference number allocated to the initial report, if this is known

'Unapproved' biologicals granted access through an exemption scheme have different reporting requirement (see Reporting requirements for biologicals supplied through an exemption scheme).

When you must report

We refer to the day the 'clock' starts for reporting as Day 0.

Reporting timelines are based on **calendar days**, including weekends and public holidays, and relate to the **Australian sponsor**.

The timeframes for reporting serious threats to public health and adverse events related to biologicals are specified in section 16AB of the *Therapeutic Goods Regulations 1990* and can be summarised in the table below.

Timeframes for reporting

Report type	Timeframe
Serious threat to public health	≤ 48 hours
Serious adverse event (in Australia)	≤ 10 calendar days
Near serious adverse event	≤ 30 calendar days

You must report:

- within 48 hours of becoming aware of an event or occurrence that represents a serious threat to public health
- within 10 days of becoming aware of an event or occurrence that led to the death or serious deterioration in the state of health of a patient, a user of the biological or another person (serious adverse event)
- within 30 days of becoming aware of an event or occurrence that, if it occurred again, may lead to the death or serious deterioration in the state of health of a patient, a user of the biological or another person (near serious adverse event)

Issues related to quality defects are to be reported as soon as possible.

Timeframes will be provided for Periodic Safety Update Reports (PSURs) and when the TGA requests specific information.

Timeframe for reporting a serious and near serious adverse event

You must report serious and near serious adverse events to the TGA as soon as possible and no later than 10 and 30 calendar days, respectively, from receipt.

The reporting timeframe begins on the day that the minimum four data elements (patient, biological, event and reporter) that constitute a valid adverse event report are received by any personnel of the sponsor—including sales representatives and contractors.

Where you have entered into a relationship with a second company for the marketing of, or research on, the suspected biological, Day 0 is as soon as any personnel of the primary sponsor (i.e. the sponsor who holds the ARTG number for the biological) receives the minimum information. The timeframe for regulatory submission should be no longer than 10 or 30 days calendar days from first receipt by the second company and explicit procedures and detailed agreements should exist between you and the second company to facilitate achievement of this objective.

Follow up information

The reporting time clock restarts when any of the sponsor's personnel receives additional clinical or medically relevant information for a previously reported serious or near serious adverse event.

Only significant follow-up information must be reported to the TGA, for example, new information for a case that results in a re-classification from non-serious to a serious or near serious adverse event. The reporting timeframe starts from the date of re-classification.

Adverse events from literature

Where the adverse event is identified through screening the worldwide literature, the clock starts when you become aware of a publication of reports of cases which occurred in Australia and contain at least the minimum four data elements.

You may use the services of an external party to conduct searches of the published scientific and medical literature; however, you remain responsible for the performance of the search and subsequent reporting. Day 0 is when anyone, either of the sponsor or the contractual partner (whichever is the earliest), becomes aware of a publication containing the minimum information. The transfer of a pharmacovigilance task or function should be detailed in a contract between you and the service provider, in order to ensure that published literature cases are reported as required within the correct timeframes. Where a third party provides a review or a collated report from the published scientific and medical literature, Day 0 is the date the search was run (provided the minimum criteria are available in the abstract), and not the date the information was supplied to your company.

Timeframe for reporting a serious threat to public health

You must report serious threats to public health to the TGA as soon as possible and no later than 48 hours of you receiving notice of them.

The 48 hour clock starts (Day 0) from the time any of your personnel —including any third parties, vendors or partners that have been delegated pharmacovigilance responsibilities of the sponsor—becomes aware of the issue. This is considered to be as soon as:

- your review and analysis has determined that a serious threat to public health exists (which is not necessarily after completion of an investigation)

OR

- when you become aware of the safety actions of a comparable overseas regulatory agency

If you are unsure as to whether the incident should be classified as a serious threat to public health, or in cases where internal processes may result in a delay in submitting a written report, we recommend that the TGA be contacted within 48 hours.

How to report serious and near-serious adverse events

Validation of adverse event reports

You are expected to validate all serious and near serious adverse event reports before submitting them to us within the specified timeframes. A validated report contains the minimum four data elements (patient, substance, event and reporter). The reporting timeframe does not begin until the report is valid.

Minimum information for a valid report

Adverse event reports are valid if the following information exists:

1. one or more identifiable reporters (the primary source)
   - the primary source is the person who reports the matter to the sponsor. There may be several primary sources who provide information on the same case, including health professionals and consumers. In this situation, provide us with all the primary sources' details, including their qualifications
2. an identifiable patient
3. one or more suspected biologicals, delivery system or other aspect of a biological
4. one or more suspected adverse events (events with a reasonable possibility of causal relationship)

Identifiable reporters and patients

Identifiable means you can verify the existence of a real patient or a reporter:

- Û Do not include the full name of the patient in your report to us
- Ü Include patient initials or a patient identification number
- Ü Only provide us with the name and contact details with the reporter's agreement

The adverse event is still valid providing you are able confirm the case directly with the reporter, even if the reporter does not agree to their contact details being provided to the TGA.

It is important that you identify the patient and the reporter to avoid case duplication and fraudulent reporting, and allow appropriate cases to be followed up. With second-hand reports, make every reasonable effort to verify the existence of an identifiable patient or reporter.

Follow up cases to obtain the minimum four data elements and detailed supplementary information relevant to the scientific evaluation of the adverse event(s).

If you choose to report an adverse event without the minimum information required for validity, your report must include the biological substance or product name provided by the primary reporter.

Invalid reports

Information that does not need to be reported individually to us includes:

- reports for which the minimum information is incomplete
- adverse events for which there is not a reasonable possibility of causal relationship, such as if the primary source has made an explicit statement that a causal relationship between the biological and the adverse event has been excluded and you agree
- when a patient experienced an unspecified adverse event but no information was provided on the type of adverse event
- when only an outcome (or consequence), such as hospitalisation or death, is notified and
  - no further information about the clinical circumstances supporting the suspicion of an adverse event is provided
  - the primary source has not indicated a possible causal relationship between the outcome and the suspected biological

A report of sudden unexplained death in a patient who had been treated with a biological would usually be considered as a case of suspected adverse event and reported.

A report that is determined to be invalid may still provide pertinent safety information. All of the above information should be recorded within your biovigilance system for use in on-going safety evaluation activities.

Following up adverse event reports

You are expected to exercise diligence in following up cases to collect missing data elements.

Follow-up is required to:

- validate an initial report
- obtain detailed supplementary information significant to the scientific evaluation of the cases

You should validate all serious and near serious adverse event reports and provide all clinical and medically relevant information that becomes available to the TGA. You should tailor follow-up methods towards optimising the collection of missing information. This should be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a particular safety concern.

Particular effort should be taken to obtain as many details as possible for:

- monitored events of special interest
- prospective reports of pregnancy, where reports of pregnancy following the use of the biological are monitored until the outcome of the pregnancy is known
- reports of adverse events during pregnancy
- cases notifying the death of a patient
- cases reporting new risks or changes in known risks
- reports associated with overdose, abuse, off-label use, misuse, administration error or occupational exposure—information in these cases needs to be as complete as possible with regards to early symptoms, treatments, outcomes and context of occurrence (e.g. error in prescription, administration, dispensing, dosage, unauthorised indication or population etc.)

You should document your attempts to obtain follow-up information.

Once a case has been reported, additional information should be provided as a follow-up report. Follow-up reports should include the TGA adverse event (ADRS) number allocated to the initial report and the additional information should be clearly identified.

Following up consumer reports

Reports from consumers are a valuable source of information. You should document all adverse event reports from consumers in the same way as you would document adverse event reports from any other source and you should take consumer reports into account in overall safety assessments.

If a consumer reports an adverse event, you should encourage the consumer to talk to their health professional to ensure they are provided with any necessary medical attention. You should also seek and document permission from the consumer to allow contact with the treating doctor to obtain confirmation and additional relevant medical information, which will then be included in the report to the TGA.

The report to us should state that the reporter is a consumer; however, we do not require the reporter's name or contact details as long as you are able to contact the reporter to obtain further information.

It is important to ascertain the seriousness of the event. For a non-serious adverse event, additional follow-up or medical confirmation may not be necessary. For serious events you are expected to make reasonable attempt to obtain voluntary informed consent to contact the treating doctor, or to obtain the relevant medical documentation directly from the consumer so that causality can be assessed.

Data elements to include in adverse event reports

We recommend that you try to collect and include as many of the below key data elements as are pertinent to the case in the report so it can be assessed. Some information might not be relevant, depending on the circumstances. However, initial reports should contain at least the minimum four data elements.

Patient details

Do not tell us the names of individual patients for privacy reasons.

Provide the following patient details:

- initials
- other relevant identifiers (patient number, for example)
- gender
- age, date of birth or age category (e.g. adolescent, adult, elderly): see Use in paediatric or elderly populations
- concomitant conditions, including pregnancy
- medical history including relevant smoking, alcohol and illegal drug history
- relevant family history
- ethnicity
- weight and height of patient

For a parent-child or parent-fetus report:

- the gestation period at time of exposure
- information concerning the parent, such as:
  - parent identification
  - parent age or date of birth
  - last menstrual period date for mother
  - weight
  - height
  - gender
  - relevant medical history and concurrent conditions
  - relevant smoking, alcohol and illegal drug history

Details of the biological(s)

- brand name
- International Non-Proprietary Name (INN) or Australian Cell and Tissue Name (ACN)
- active ingredients:
  - for combination biologicals that include a delivery system and more than one ingredient, each active ingredient should be listed
  - if the primary source suspects a possible causal role of one of the ingredients, this information should be provided in the report
- batch or lot number
- ARTG number
- indication(s) for which the biological was used
- dosage form
- dose (specify units if available) and regimen if relevant
- route of administration (or parent route of administration in cases of a parent-child or parent-fetus report)
- starting date and time
- if relevant, duration of treatment and stopping date and time
- actions taken with the biological, such as:
  - implant withdrawn
  - antidote administered
  - other treatment given
  - no action
  - unknown
  - not applicable
- any additional information about the biological
- if the adverse event is suspected to be the result of an interaction between a biological and another substance or product, for example, another biological, a medicine, food, alcohol, illegal drugs or a medical device

Other treatment(s)

Provide the same information as in Details of the biological(s) for the following:

- concomitant medicines including non-prescription, over-the-counter medicines, herbal remedies, dietary supplements, complementary and alternative therapies et cetera
- relevant medical devices

Details of adverse event(s)

- a full description of the event(s), including body site and severity
  - preferably, use the appropriate Lowest Level Terms from the Medical Dictionary for Regulatory Activities (MedDRA)
- the event as reported by the primary source
  - provide the original words that were used by the reporter to describe the adverse event(s)
- the criteria for regarding the report as serious
- description of the reported signs and symptoms
- specific diagnosis for the event(s)
- onset date (and time) of event(s)
- stop date (and time) or duration of event(s)
- time interval between administration of the suspect biological and start of event(s)
- relevant diagnostic test results and laboratory data
- setting e.g. hospital, out-patient clinic, home, nursing home
- outcome of event(s) at the time of last observation e.g. recovered or resolved, recovering or resolving, not recovered or not resolved, recovered or resolved with sequelae—describe sequelae
- if death occurred:
  - date of death
  - whether autopsy was performed
  - relevant autopsy or post-mortem findings, including coroner's report
  - stated cause of death
- assessment of the relatedness of the product to the event(s):
  - source of assessment e.g. initial reporter, investigator, regulatory agency, sponsor
  - method of assessment: global introspection, algorithm, Bayesian calculation
  - result of assessment
  - whether you consider there to be a causal association between the suspect product(s) and event(s) and provide the criteria on which you have made your assessment
- where possible, provide a case narrative for the adverse event(s)—present this in a logical time sequence of the patient's experience including:
  - clinical course
  - therapeutic measures
  - outcome
  - other relevant information

The information provided in the narrative should be consistent with the data in other parts of the report.

- sponsor's comments e.g. diagnosis, syndrome, reclassification of event(s)
- whether the case was medically confirmed. Where the report was made by a consumer, the following is sufficient to consider the report as medically confirmed:
  - provision by the consumer of medical documentation, such as laboratory or other test data, that supports the occurrence of the suspected adverse event(s) or that indicates that an identifiable health professional suspects a reasonable possibility of causal relationship between the biological and the reported adverse event(s)
  - if the consumer initially reports more than one event and at least one receives medical confirmation, then the whole report should be documented as a spontaneous report that has been medically confirmed
  - if the report is submitted by a medically qualified patient, friend, relative or carer, the case should be considered as medically confirmed

Reporter details

û Unless the reporter has given you permission, do not tell us identifying information about the reporter.

- the name of the reporter
- email address
- postal address, including postcode
- telephone number
- fax number
- reporter type (consumer, health professional etc.)
- for health professionals, the profession (specialty) or the name of the professional association or other group of which they are a member
- for non-health professionals, any professional qualification e.g. lawyer

All parties who provide case information or are approached for case information should be identifiable, not just the primary source. Identification refers to the verification of the existence of the parties and their knowledge of the case.

A primary source is a person who reports the facts to you or another agency. Sometimes there are several primary sources for an adverse event, such as several health professionals or several consumers who provide information on the same case. In this situation, you should provide details of all primary sources, including their qualifications, in the case report. Reports on the same case provided directly to us from more than one primary source will be regarded as duplicates.

Administrative and sponsor details

- source of report (spontaneous, epidemiological study, patient survey, literature etc.)
- date the event report was first received by the sponsor
- country in which the event occurred
- type of report: initial or follow-up (if follow-up, provide the TGA adverse event [ADRS] number allocated to the initial report)
- name and address of sponsor
- name and contact details of the person who is taking responsibility on behalf of the sponsor for the accuracy and veracity of the information in the report
- sponsor's identification number for the case (the same number should be used for the initial and follow-up reports on the same case)
- the TGA adverse event (ADRS) identification number(s) (if known) of possible duplicate reports initially submitted by a consumer or health professional

Format of adverse event reports

All reports need to be in writing and in English. Text should be legible and preferably in Times or Arial font, with a font size no less than 10 point. If text is in a font size less than 10, then the report should be posted or emailed, not faxed. Reports should not be photo-reduced or condensed, because the TGA needs to be able to produce legible copies of reports.

All reports need to identify the name and contact details of the person in Australia who is taking responsibility on behalf of the sponsor for the accuracy and veracity of the information in the report. It is preferable for the nominated contact person for biovigilance to submit all reports.

We will advise you if a report format is considered to be unacceptable.

A detailed description of what should to be included in reports of serious and near serious adverse events is in Data elements to include in reports.

Submitting adverse event reports

We prefer that adverse event reports are submitted electronically as structured data with the use of controlled vocabularies for the relevant data elements where applicable. This enables information to be entered into our database more easily, and enables international cooperation over safety issues.

Reports of adverse events may be in free text, or you may use one of a number of different forms that are available:

- online through the TGA Australian Adverse Drug Reaction Reporting System
- E2B formatted reports can be submitted to e2b.reports@tga.gov.au
- blue card adverse reaction reporting form
- form provided by CIOMS (Council for International Organizations of Medical Sciences) to adr.reports@health.gov.au

The following CIOMS publication is useful: *Reporting adverse drug reactions: definitions of terms and criteria for their use*.

Providing publications

When a publication is the source of information about a serious or near serious adverse event or other safety information, then this publication needs to be provided to us, preferably at the same time as the initial report. If the publication is not in English, then you should provide a summary or translation in English.

If the article is not available at the time of the initial report, then it must be provided to us within the following timeframes:

- within 10 days of submission of a serious adverse event report
- within 30 days of submission of a near serious adverse event report

If it will be difficult to meet the specified timeframe, notify us in writing prior to the end of the specified period.

Contact details

Once a biological is included in the ARTG, report adverse events to the Pharmacovigilance and Special Access Branch at the TGA.

Privacy

We do not wish to have the names of patients on record; we only require information that is necessary for us to perform our functions. General privacy information is available on our website.

Our requirements do not override applicable privacy laws. You should be familiar with and discharge your obligations in relation to the collection, use and disclosure of personal information in accordance with the Australian Privacy Principles as set out in the *Privacy Act 1988* and any applicable state and territory privacy legislation.

Personal information is often collected to assist in the post-market monitoring of the safety of therapeutic goods under the *Therapeutic Goods Act 1989*. We collect personal information in reports of adverse events and safety issues related to biologicals to:

- assess the safety of biologicals under the *Therapeutic Goods Act 1989*
- contact the reporter of the adverse event if further information is required
- contact representatives of entities that supply therapeutic goods, to discuss reported adverse events
- check that the same information has not been received multiple times for the same adverse event

At times, this information is collected from someone other than the individual to whom the personal information relates. This can occur when an adverse event is reported to a person or an entity other than the TGA (such as a health professional or a hospital) and that person or entity passes the information on to us.

Personal information collected may be disclosed by consent or where the disclosure is required by, or authorised under, a law (for example, under section 61 of the Therapeutic Goods Act 1989).

How to report a serious threat to public health

You must report a serious threat to public health within 48 hours of becoming aware of an event or occurrence that represents a serious threat to public health.

Reports of serious threats to public health need to be in writing and preferably sent by email to the Signal Investigation Coordinator (si.coordinator@health.gov.au).

All emails will receive an automated response as an acknowledgement of receipt.

We ask that for such reports:

- the subject line is 'Urgent – serious threat to public health – [descriptor: name or number of biological, name of sponsor, or some other descriptor]'
- describe the evidence for the threat
- indicate the action that you are proposing to take to eliminate or reduce the risk
  - the action may relate to conditions of inclusion in the ARTG including amendments to the label or the product information or any other change
  - no action should be accompanied with justification
- clearly identify the person in Australia who is taking responsibility on behalf of the sponsor for the accuracy and veracity of the information in the report
- include contact details of the person reporting on behalf of the sponsor, who is preferably the nominated biovigilance contact person

Where the serious threat to public health is identified from an increase in the frequency of serious adverse events, you should provide in the report the data used to derive the frequency estimate, including the total number of adverse event reports and the total number of individuals exposed.

If requested by the TGA, you must be able to:

- provide within the specified time frame any additional information to assist with the evaluation of benefits and risks of the biological, including information about the extent of use of the product concerned
- provide copies of overseas adverse event reports in your possession that formed the basis for actions undertaken by an overseas regulator

Special situations and reporting requirements

Supply through an exemption scheme

There are different reporting requirements when a biological is not being used through its inclusion in the ARTG but is being used because access has been granted through an exemption scheme, such as the Special Access Scheme, Authorised Prescriber Scheme and Clinical Trials Scheme.

Special Access Scheme

The procedures for reporting of adverse events for biologicals accessed under the Special Access Scheme is outlined in *Access to unapproved therapeutic goods - Special Access Scheme*.

Authorised Prescriber

The procedures for reporting of adverse events for biologicals accessed under the Authorised Scheme are outlined in *Authorised Prescriber Scheme—Guidance for Medical Practitioners, Human Research Ethics Committees, Specialist Colleges and Sponsors*.

Clinical trials for unapproved indications

For reports from clinical trials in Australia where the biological is being used outside the approved indications or intended use, refer to:

- Access to unapproved therapeutic goods – Clinical trials in Australia
- Note for guidance on clinical safety data management: Definitions and standards for expedited reporting CPMP/ICH/377/95

Between inclusion application and granting of ARTG inclusion

Consideration by the Advisory Committee on Biologicals

If an application is to be considered by the Advisory Committee on Biologicals, you should submit with your pre-committee response a tabulation of any serious unexpected adverse events not mentioned in the proposed Australian product documentation or not already submitted.

Between the pre-committee response and ARTG inclusion

Following the pre-committee response, you should report serious adverse events and serious threats to public health according to the same timeframe as they would be reported if the product was included in the ARTG. However, please send these reports to the TGA area responsible for biologicals, **not** the Pharmacovigilance and Special Access Branch.

Withdrawal or lapse of application

When an application for inclusion of a biological in the ARTG is withdrawn or lapses, section 32DR of the *Therapeutic Goods Act 1989* provides that the Secretary of the Department of Health may require you to disclose whether certain information about the product is known to you and, if that is the case, to provide that information to the Secretary.

Post-ARTG inclusion trial data

studies undertaken in Australia that are assessed by the reporting healthcare professional, the investigator or you as having at least a possible causal relationship with the biological.

A post-ARTG inclusion study is any study carried out in accordance with the conditions of inclusion of a biological in the ARTG, label indications or product document indications. This includes studies that may have commenced prior to approval and are ongoing after the product has been included in the ARTG. A post ARTG-inclusion study may sometimes also fall within the definition of a safety study.

Such a study may be carried out:

- as a condition of ARTG inclusion of that biological
- by you or an external researcher.

You are **not** required to report as individual cases:

- adverse events not suspected of being due to the biological
- blinded cases
  - report serious adverse events only if the blind has been broken or when un-blinding occurs at the end of the study

For guidance on the management of blinded cases, refer to Section D of the *Note for guidance on clinical safety data management: Definitions and standards for expedited reporting* (CPMP/ICH/377/95).

For post-ARTG inclusion studies conducted or initiated by an independent investigator (i.e. non-company sponsored studies), the investigator is responsible for reporting adverse events to the TGA. However, if you are aware of the study, then we recommend that you request the investigator to notify you of adverse events that occur in the study.

During other post-market initiatives

You may be undertaking other post-market initiatives that collect information related to your products. These include, but are not limited to:

- patient support and disease management programs
- surveys of patients, health professionals or health providers
- information gathering on efficacy or patient compliance
- market research programs
- compassionate use or named patient use programs
- registries

These activities may involve the receipt of information about adverse events. You are expected to have a system in place to collect full and comprehensive case information and to evaluate that information to determine whether these adverse events are possibly related to your biological.

For solicited adverse event reports, you are required to assess causality to determine whether they should be submitted to the TGA.

Overseas adverse events

You are not required to submit individual reports of serious, near serious or non-serious adverse events for your product that occur in countries other than Australia. However, you are expected to:

- keep records of such adverse events
- provide the report to the TGA if requested
- consider the report in future Periodic Safety Update Reports (PSURs), if PSURs are required
- include the report in your analyses of global adverse events.

Where such adverse events impact on the benefit-risk balance or overall safety profile of the biological, you need to report the information as a serious threat to public health.

Australian products marketed overseas

For a biological manufactured in Australia and marketed overseas, you as the Australian sponsor are expected to request that any information on suspected adverse events in other countries is brought to your attention by the overseas sponsors in a timely manner. You are not required to report individual adverse events that have occurred overseas to the TGA but you must include overseas events in your ongoing monitoring of the product and report to us as a serious threat to public health if analysis of the events indicates a change in the benefit-risk of the product.

Overseas products marketed in Australia

Some biologicals included in the ARTG and marketed in Australia may be manufactured overseas and marketed by different sponsors overseas. Regardless of where it is manufactured, you are responsible for meeting the regulatory biovigilance requirements for your products.

In these cases, you as the Australian sponsor should also have a commercial agreement with the overseas sponsors so that you are provided with details in a timely manner of any adverse events that have occurred overseas. You are not required to report individual adverse events that have occurred overseas to the TGA but they must include overseas events in your ongoing monitoring of the product and report to us as a serious threat to public health if analysis of the events indicates a change in the benefit-risk of the product.

Use in pregnancy and breastfeeding

You should follow up on all individual reports of pregnancies where the fetus could have been exposed to a biological so that information on the outcome of the pregnancy and development of the child after birth can be collected. You should consider possible exposure through the mother or the father.

The likelihood of a biological administered to a parent contributing to a short-term or long-term adverse effect on a fetus or newborn should be considered on a case-by-case basis.

Reports of adverse events related to exposure to a biological during pregnancy should contain as much detail as possible to help you with assessing the causal relationship between a reported adverse event and the exposure.

Teratogenicity is a serious threat to public health

A signal of a possible teratogenic effect is considered to be a serious threat to public health and must be reported in accordance with the timeframe for reporting a serious threat to public health.

Such a signal might come from a cluster of similar abnormal pregnancy outcomes in clinical situations.

Serious adverse events occurring during pregnancy or breastfeeding

If you become aware of individual cases where a pregnancy results in an abnormal outcome that the reporting health professional considers might be due to a biological, then this is a reportable serious adverse event. This includes:

- congenital anomalies (e.g. birth defect, deformity, premature birth) or developmental delay in the fetus or child
- foetal death and spontaneous abortion
- suspected adverse events in the neonate that are classified as serious

Suspected serious adverse events that occur in infants following exposure to a biological via breast milk are also reportable.

Other events during pregnancy

Cases that are **not** to be reported routinely to us because there is no suspected adverse event include:

- induced termination of pregnancy without information on congenital malformation
- pregnancy exposure without outcome data
- pregnancies that have a normal outcome

However, you are expected to collect these reports and provide them to us if requested. If a Periodic Safety Update Report (PSUR) is required, these reports should be included together with aggregated data of overall exposure and details of normal, abnormal and unknown outcomes. We may also request reports from prospective pregnancy registries to be included and evaluated in the PSUR.

Use in paediatric or elderly populations

The collection of safety information in paediatric and elderly populations is important to assist in identifying potential safety signals specific to particular age groups.

You should make reasonable attempts to obtain and submit the date of birth or the age of the patient when a serious or near serious adverse event is reported. If the reporter does not wish to specify the exact age, try to obtain an age group.

Overdose, abuse, off-label use, misuse, administration error or occupational exposure

You are expected to follow up on all individual reports of serious or near serious adverse events in Australia associated with overdose, abuse, off-label use, misuse, administration error or occupational exposure. Information in these cases needs to be as complete as possible with regards to early symptoms, treatments, outcomes and context of occurrence (e.g. prescription errors, administration, dispensing, dosage, unauthorised indication or population etc.).

You must report all such cases associated with serious adverse events or near serious adverse events in Australia to us in accordance with the regulatory timeframes.

When such reports constitute serious threats to public health impacting on the benefit-risk balance of the biological, they must be reported in the timeframe for reporting a serious threat to public health.

When there is no associated adverse event, or the associated adverse event is non-serious, these cases are not to be reported routinely to the TGA. Reports of such incidents should be collected and included in ongoing review and analysis of the biological, and be provided on request to the TGA.

Recalls, quality defects and contaminated or counterfeit biologicals

You must notify us of suspected or confirmed quality defects and contaminated or counterfeit biological with the least possible delay in accordance with the Uniform Recall Procedure for Therapeutic Goods (URPTG). This procedure is a result of consultation between the therapeutic goods industry and Commonwealth, state and territory health authorities.

Notification needs to be prompt because it may be necessary to implement urgent measures, such as the recall of one or more defective batch(es) of a biological from the market, to protect public health.

To notify us of any recalls, quality defects and contaminated or counterfeit biological, you may use the Human blood and tissues recall report form. For problems requiring urgent attention, you may also telephone TGA Recalls.

You are expected to have a system in place to ensure that reports of adverse events suspected of being related to quality defects of a biological or an adulterated or counterfeit biological are investigated in a timely manner.

In addition to reporting a suspected or confirmed quality defect or an adulterated or counterfeit biological, all serious adverse events or serious threats to public health associated with the quality defect need to be reported within the required timeframes.

It is important to note that recall actions encompass not only recalls, i.e. removal from supply or use from the market, but also includes recall for product correction or hazard alert.

Transmission of an infectious agent

Unexpected transmission of an infectious agent may constitute a serious threat to public health. You need to use clinical judgement to determine if cases of transmission of infectious agents are considered serious threats to public health.

Infectious agents include:

- bacteria
- viruses
- infectious particles such as prions
- fungi
- protozoa
- helminths

Transmission of an infectious agent may be suspected from clinical signs or symptoms or laboratory findings. In ascertaining the type of infection, you should focus on the agents known to be potentially transmitted by a biological, but should also consider unknown agents and reactivation of any viral vector.

When considering contributors to the transmission, you should take care to distinguish (if possible) the:

- cause (e.g. injection or other administration)
- source (e.g. the tissue donor or contamination)
- clinical condition of the patient (e.g. immunosuppressed or recently vaccinated)

Confirmation of contamination of the biological increases the evidence for transmission and may suggest a quality defect for which action should be taken. In this context, 'contamination' includes inadequate inactivation or attenuation of infectious agents known to be present.

Unexpected lack of efficacy

An unexpected lack of efficacy may be a serious adverse event or a serious threat to public health, or neither. Clinical judgement should be used when considering if cases of lack of therapeutic efficacy qualify for reporting, and if so, as serious adverse events or as serious threats to public health.

Examples of serious adverse events relating to lack of efficacy reports of a biological include:

- where the biological is used to treat a critical condition or a life-threatening disease, unless the person reporting to you has specifically stated that the outcome was due to disease progression and was not related to the biological
- if the lack of efficacy is thought to have contributed to a change in or modification (for instance, aggravation, progression or recurrence) of the condition for which the biological was administered. The report should include the nature of the effect on the medical condition

In all cases, you should record lack of therapeutic efficacy of a biological and perform follow-up if the report is incomplete. You are expected to retain all reports of cases not considered to qualify as serious adverse events and to provide them if requested and consider them in the next Periodic Safety Update Report (PSUR), if PSURs are required.

Lack of efficacy may flag a change in:

- the quality of manufacturing
- a property of the biological
- responsiveness to the biological

We expect you to take all reasonable steps to investigate these possibilities. If the investigation concludes that such a change has occurred, you must report the issue as a serious threat to public health. If a quality defect is identified, you must also report this as soon as possible as detailed in Reporting recalls, quality defects and contaminated or counterfeit biologicals.

Non-serious adverse events

You do not need to routinely report non-serious adverse events to the TGA. If these occur in Australia, you should keep records of such events and:

- report them, if specifically requested by the TGA, in the requested format and timeframe
- include them in ongoing monitoring activities including in signal investigation processes
- consider them in future Periodic Safety Update Reports (PSURs), if PSURs are required

If later information regarding a non-serious case results in a reclassification to a serious or near serious adverse event, then the reporting timeframe starts from the date of reclassification.

Periodic Safety Update Reports (PSURs)

A Periodic Safety Update Report (PSUR) is a systematic review of the global safety data that becomes available to the sponsor of a marketed product during a specific time period. PSURs are produced in an internationally agreed format. PSURs are also referred to as Periodic Benefit-Risk Evaluation Reports (PBRERs).

The objective of a PSUR is to present a comprehensive and critical analysis of the benefit-risk balance of a therapeutic good taking into account new and emerging information in the context of cumulative information on benefits and risks.

PSURs are required to be submitted at defined time-points for:

- all Class 4 biologicals
- all Class 3 biologicals
- some Class 2 biologicals (when imposed under section 32ED of the *Therapeutic Goods Act 1989*)

The frequency of PSURs is specified in the non-standard conditions of approval for Class 3 and Class 4 biologicals and in the conditions of inclusion in the ARTG for Class 2 biologicals. The report is to be submitted to us within 90 days of the data lock point, which is the date after which no further data is included in the PSUR.

For more information on PSURs, refer to the EMA guideline EMA/816292/2011 Rev 1* (9 December 2013) *Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report*.

Your record-keeping requirements

You must retain records pertaining to the reporting requirements and safety of your biological (section 5 of the *Therapeutic Goods (Biologicals—Conditions of Inclusion in Register) Determination 2017)*. Information relating to biovigilance activities and the safety of the biological include, but is not limited to:

- all adverse event reports (serious, near-serious and non-serious)
- information surrounding serious threats to public health
- special situation reports including, but not limited to, reports:
  - from post-registration studies
  - from post-marketing initiatives
  - of exposure during pregnancy and breastfeeding
  - of use in paediatric or elderly populations
  - of lack of efficacy
  - of quality defect issues
  - of transmission of infectious agents
  - of overdose, abuse, off-label use, misuse, medication error or occupational exposure
  - of non-serious adverse reactions and reactions occurring overseas
  - relating to suspended or discontinued products
- reference safety documents and non-valid reports containing biological-event pairs

These must be kept for as long as the product is approved for inclusion in the ARTG and for a period of **10 years after removal from the ARTG**.

General safety information on your biological should also be retained for as long as the product is approved for inclusion in the ARTG. This includes, but is not limited to:

- ongoing monitoring activities
- PSURs
- literature reviews
- contracts with biovigilance providers
- documentation regarding changes to reference safety information
- biovigilance procedural documents
- biovigilance training documents

Your biovigilance system

A biovigilance system is used to fulfil the tasks and responsibilities associated with the detection, assessment, understanding and prevention of adverse effects of biologicals. It needs to be designed to monitor the safety of authorised biologicals and detect any change to their benefit-risk balance.

A biovigilance system is not in itself required by Australian legislation, but such a system is required for you to be able to meet legislated requirements for reporting adverse events and serious threats to public health.

A biovigilance system will:

- allow you to take responsibility and liability for your products
- ensure appropriate action is taken when necessary

Where a risk management plan (RMP) is required, the biovigilance system must support your ability to undertake the biovigilance activities described in the plan. An RMP is usually a requirement for new applications for class 3 and 4 biologicals and selected class 2 biologicals (see Risk management plans for medicines and biologicals – Australian requirements and recommendations).

Objectives of a biovigilance system

Your biovigilance system needs to enable you to undertake:

- all routine biovigilance requirements described in these guidelines
- any additional biovigilance activities required through the RMP (if an RMP is required)
- all traceability and other biovigilance requirements imposed on you through Therapeutic Goods Orders, an RMP or as conditions of registration
- the investigation and reporting of product quality issues
- the critical analysis of adverse events and other safety and quality information
- any activities needed to mitigate an identified safety issue

Biovigilance contact person

You should nominate a biovigilance contact person in Australia for all of the biologicals you sponsor. This person will be our primary contact to direct requests for biovigilance information and is responsible for reporting and coordinating biovigilance communication between you and the TGA.

You can nominate the biovigilance contact person via the TGA Business Services site. For further assistance, please contact the TBS Helpdesk.

We ask that you notify us of the biovigilance contact person:

- within 15 calendar days of a product being entered in the ARTG

AND

- within 15 calendar days of any change in details of the nominated contact person

Please note that the biovigilance contact person may be different to the person responsible for biovigilance in Australia, although ideally they are the same person.

Person responsible for biovigilance in Australia

Every sponsor is legally responsible for meeting biovigilance requirements for their products, even if their products are the same as products belonging to other sponsors. You should have a person who takes responsibility for biovigilance of your biologicals in Australia. This person can also be the biovigilance contact person and should ensure that you comply with biovigilance legislation and have an effective biovigilance system in place.

We recommend that this person:

- lives in Australia
- is permanently and continuously available (or at least within the hours of 9am–5pm AEST Monday to Friday), with a back-up person appointed should the primary person responsible for biovigilance be absent. Please note this means the person is contactable when required, e.g. by phone, and not necessarily on-site full-time. Ultimately, sponsors need to be confident that the person responsible for biovigilance can be reached to seek advice in emergency situations
- is trained or experienced in biovigilance and relevant legislation in Australia
- is medically qualified, or if not, have ready access to a medically qualified person for any clinical assessments necessary. We prefer that this medically qualified person resides and is medically registered in Australia so they can address adverse events, serious threats to public health and the benefit–risk balance of biologicals in the Australian context

The person responsible for biovigilance in Australia should be suitably experienced and qualified in order to monitor the safety of your biologicals. The characteristics and skills of the individual should be dependent on their specific roles and responsibilities and enable you to meet your biovigilance requirements.

The person responsible for biovigilance in Australia needs to have adequate understanding of the Australian and global (where applicable) biovigilance processes in order to allow them to have effective oversight of the entire biovigilance system.

Adverse event recording and reporting

For recording and reporting adverse events, your biovigilance system should:

- ensure that collected reports are authentic (verifiable), legible, accurate, consistent and as complete as possible for clinical assessment
- be structured to enable serious adverse event reports to be validated in a timely manner and submitted to the TGA within the legal reporting timeframes
- enable you to provide within a specified timeframe any additional information requested by the TGA to assist with evaluation of the benefits and risks of a biological, including information about the volume of sales or prescriptions of the product concerned

Traceability of biologicals

You are required to be able to trace a biological from donor to product release [Therapeutic Goods Order (TGO) No. 87, subsection 6(1)]. For higher risk biologicals that require an RMP, a product-specific condition of registration is included that requires product traceability from the donor to the recipient.

Procedures are to be documented for tracing products from donor to recipient and from recipient to donor, so that disease transmission between donor and recipient can be investigated. You should be able to match donor reference numbers with batch or lot numbers of the released biological, and biologicals that are released for specific patients. Batch or lot numbers should be included in the medical records and in some cases on patient cards to facilitate adverse event reporting.

It is important that you can locate and identify a biological at any stage including when in:

- donor
- procurement
- processing
- testing
- storage
- distribution to the recipient
- disposal

The donor, tissue establishments, manufacturing facilities, medical facilities and recipients must all be identifiable.

Traceability also covers the ability to locate and identify all relevant data relating to products, materials and people that have come into contact with the biological.

Related information and guidance

- Risk management plans for medicines and biologicals – Australian requirements and recommendations

Analysis of safety information

Biovigilance does not just consist of collection, but also of scientific evaluation and critical analysis of adverse event reports and any other safety issues associated with the biological. Safety issues arise from adverse event reports, but also arise from more general situations and may occur at any stage in the development, manufacturing, administration or follow-up of a product. Your system should enable you to detect and investigate safety issues.

Signal detection

You need to have systems in place to detect safety signals. Such signals arise from one or multiple sources (including observation and experiments) and suggest a new potentially causal association or a new aspect of a known association, between the biological and an event or set of related events.

Signal investigation

You should actively investigate signals you judge to be of sufficient likelihood of being true associations to determine whether they can be verified or refuted. If a verified signal may change the benefit-risk profile of a biological, you must report it to the TGA as a serious threat to public health.

A useful resource is *Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII.*

Monitoring and collecting safety information

A biovigilance system should encompass the monitoring and collection of information from as many sources as possible.

Information relating to the safety of your biological can be identified from a variety of sources including:

- reports made directly to you by health professionals or consumers
- worldwide scientific and medical literature
- reports in internet and digital media
- reports from non-medical sources
- post-ARTG inclusion studies
- other post-market initiatives

You should have mechanisms in place to collect full and comprehensive case information from all sources and to evaluate that information in a timely manner.

Reports made to you

Information on all suspected adverse events reported to you or people who work for or have a contractual relationship with you (such as medical and sales representatives, vendors, marketing organisations, partners and contract manufacturers) is to be collected, collated, analysed, followed up and held so that it may be accessed at a single point within Australia.

Worldwide literature

The medical and scientific literature is a significant source of information for the monitoring of the safety profile and risk-benefit balance of biologicals and for the detection of new safety signals and emerging safety issues.

You should:

- undertake regular (weekly) systematic review of the literature in widely used reference databases that contain the largest reference of scientific and medical publications in relation to the biological and its properties
- review and assess reports of adverse events from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, to identify, record and report adverse events and serious threats to public health
- ensure that, where contractual arrangements are made with a person or organisation to perform literature searches, detailed agreements exist that enable you to comply with all reporting obligations

For adverse events reported in the worldwide literature, you should endeavour to identify the cases that occurred in Australia and report these to the TGA if they are serious or near serious. When you cannot determine whether the event occurred in Australia, you should:

- keep records of the adverse events
- produce a report if requested by the TGA
- consider the report for discussion in any future Periodic Safety Update Reports (PSURs), if a PSUR is required
- consider the report in any global analysis of adverse events

Reports in internet and digital media

You should consider using your websites to facilitate the collection of adverse event reports. You can do this by providing reporting forms or contact details for direct communication. You should encourage reports from all sources, including health professionals and consumers.

Ü You should regularly screen for reports of suspected adverse events the internet (such as websites, webpages, blogs, vlogs, social networks, internet forums, chat rooms and health portals) and digital media under your management or responsibility

Û You do not need to review internet and digital media not sponsored by your company

– If you become aware of a report of a suspected adverse event described in any non-company sponsored digital medium, you should assess the report to determine whether it qualifies for reporting, and if so, you should report it within the timeframes below

For digital media **that you own**, **pay for or control**, the reporting timeframes are considered to start on the date that the information was posted. This means that screening needs to be sufficiently frequent to report:

- serious threats to public health within 48 hours
- serious adverse event reports within ten calendar days
- near-serious adverse event reports within 30 calendar days

For such reports, it is important that the reporter is identifiable, that is, you can verify the existence of a real person:

- You should make reasonable attempts to contact the reporter wherever possible to confirm the event and patient details and collect any additional information
- For serious adverse events, you may post to a public forum and request that the reporter contact you privately to provide more information

If you do not know what country the primary source is from, use the country where the information was received.

Reports from non-medical sources

You should handle a report of a suspected adverse event from a non-medical source, for example the lay press or other media, as a spontaneous report. You should make reasonable attempt to follow up the case to obtain the minimum information that constitutes a valid adverse event report and to determine the seriousness of the adverse event.

Processes

It is important to have an appropriate quality management system in place and to document all of the processes in place for the biovigilance system.

Training

Personnel undertaking biovigilance should be trained at a minimum in:

- applicable biovigilance legislation and guidelines
- privacy legislation
- report processing and evaluation

Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, marketing, legal, quality control) should be trained in adverse event collection and reporting.

Written procedures

The roles, responsibilities and required tasks of biovigilance need to be understood by and available in writing to all relevant parties.

Clear written standard operating procedures should provide for:

- quality control of the biovigilance system
- change to the biovigilance system

This is also applicable to activities that are contracted out to third parties, whose procedures the sponsor should review to verify that they are adequate and compliant with applicable requirements.

Retention of records

It is required that you retain all biovigilance documents, including records of all reports of adverse events associated with the use or administration of your biological, for as long as the product is approved for inclusion in the ARTG and for at least 10 years after it ceases to be included in the ARTG (see Record-keeping requirements).

Data quality control

Data security

You must be familiar with and discharge obligations in relation to the collection, use and disclosure of personal information in accordance with the Australian Privacy Principles under the *Privacy Act 1988,* and any relevant state or territory privacy legislation.

Electronic data and paper reports of suspected adverse events should be stored and treated in the same way as other medical records with appropriate respect for confidentiality regarding patients' and reporters' identifiability and in accordance with data privacy laws.

You should apply strict controls to documents and to databases to assure security and confidentiality of biovigilance data with access to authorised personnel only. This security extends to the complete data path.

You should implement procedures to ensure security and non-corruption of data during data transfer.

Data accessibility

Data needs to be collected, collated and held so that it may be accessed at a single point within Australia.

Data entry

It is preferable for data entry to use the appropriate Lowest Level Terms from the Medical Dictionary for Regulatory Activities (MedDRA).

Data entry staff should be instructed in the use of the terminologies, and their proficiency should be confirmed.

Quality assurance auditing, either systematically or by regular random evaluation, should verify that data is being entered correctly with the appropriate use of terminologies.

Data storage

There should to be an audit trail for electronic data. It needs to be possible to trace:

- data entry
- data modification
- dates and sources of received data
- dates and destinations of transmitted data

Handling duplicate cases

There should be a procedure to identify and manage duplicate cases at data entry and during the generation of aggregated reports.

Source data (e.g. letters, emails, records of telephone calls that include details of an event) or an image of the source data should be easily accessible. This enables initial and follow-up reports to be verified against the original data. You need to include this verification process in quality control procedures.

Data transfer

When biovigilance data is transferred within an organisation, or between organisations with contractual agreements, there should be mechanisms to establish that all notifications are received. This includes, but is not limited to, undertaking a confirmation or reconciliation process.

Biovigilance and the law

Your responsibilities

Your biovigilance responsibilities outlined in this guidance are underpinned by legislation.

Under section 32DQ of the *Therapeutic Goods Act 1989*, you **must** notify us of certain matters in relation to biologicals included in the ARTG and it is a criminal offence, or a civil penalty, to fail to make such notifications. You must report the following relevant information (section 32DQ(3)):

a. information that contradicts information already given by the sponsor under the *Therapeutic Goods Act 1989* in relation to the biological (including information given about the quality, safety or efficacy of the biological)

b. information that indicates that the use of the biological in accordance with the recommendations for its use may have an unintended harmful effect

c. information that indicates that the biological, when used in accordance with the recommendations for its use, may not be as effective as the application for inclusion of the biological in the ARTG or information already given by the sponsor under the *Therapeutic Goods Act 1989* suggests

The specified periods within which you must comply for the purposes of section 32DQ of the *Therapeutic Goods Act 1989* are prescribed in paragraph 16AB of the *Therapeutic Goods Regulations 1990*.

Privacy

You must abide by the Australian Privacy Principles set out in the *Privacy Act 1988* and any applicable state and territory privacy legislation when you collect, use or disclose personal information.

Our requirements do not override any applicable privacy laws.

General privacy information is available on our website.

Conditions

Sections 32EC and 32ED of the *Therapeutic Goods Act 1989* allow us to impose certain conditions at the time of inclusion of a biological in the ARTG and section 32EE of the *Therapeutic Goods Act 1989* allows us to impose new conditions and remove or vary existing conditions at any time while the biological remains included in the ARTG. Requirements imposed as conditions of inclusion under sections 32EC and 32ED continue to apply for biologicals where the application has been withdrawn or lapses, where the Secretary gives notice in accordance with section 32DR of the *Therapeutic Goods Act 1989*.

Under paragraph 5(a) of the *Therapeutic Goods (Biologicals—Conditions of Inclusion in Register) Determination 2017*, the legislative instrument made under subsection 32EC(2) of the *Therapeutic Goods Act 1989*, you must comply with the record-keeping requirements and the reporting requirements set out in this guidance document.

Under sections 32EF, 32EG and 32GC of the *Therapeutic Goods Act 1989*, we can cancel or suspend a biological from the ARTG for refusing or failing to comply with conditions of inclusion in the ARTG. Section 21A of the *Therapeutic Goods Act 1989* specifies the grounds for prosecuting offences related to not complying with conditions of inclusion.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication following public consultation on guidance in October 2016	Pharmacovigilance and Special Access Branch and Scientific Evaluation Branch	December 2017

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